Remarks

Introduction

Receipt is acknowledged of the Office Action dated July 26, 2001. In the Action, the Examiner has withdrawn all previous grounds of rejection under 35 U.S.C. § 112, and entered new grounds of rejection under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 112, second paragraph. The Examiner has also newly rejected the claims under alleged double patenting.

By the foregoing amendments, Applicants have amended claim 23 and added claim 104. Accordingly, claims 21-24 and 39-104 will be pending with entry of the amendments. Reconsideration and withdrawal of the outstanding rejections in view of the foregoing amendments and remarks set forth below is respectfully requested.

Amendments to Claim 23 and New Claim 104

Claim number 72 was skipped in Applicant's reply dated November 15, 1999 which newly submitted claims 38-103. Accordingly, Applicants request that after entry of the amendment and new claim 104, claims 73-104 be renumbered as claims 72-103.

Applicants have amended claim 23 to delete treatment of tumor growth and tumor metastasis. New claim 104 particularly recites a method for treating melanoma, as specifically supported at page 3, lines 9-12 of the specification.

Proprietary IDS

Applicants respectfully requests consideration of the attached Proprietary IDS in accordance with M.P.E.P. § 724.04(a) so that Applicants can, if appropriate, petition to expunge those materials pursuant to the attached petition under 37 C.F.R. § 1.59(b).

Claim Rejections under 35 U.S.C. § 112, first paragraph

On pages 3 and 4 of the Office Action, the Examiner has rejected claims 21-24 and 39-103 under 35 U.S.C. § 112, first paragraph as allegedly not enabled. Specifically, the Examiner states that "[i]n claim 23 "tumor growth" and "tumor metastasis" are generic terms that embrace many different diseases such as leukemia." The Examiner further alleges that

"[t]here is no drug which is broadly effective against all forms of tumors." Applicants respectfully traverse the rejection.

Without agreeing with the statements set forth in the rejection, but only to bring the case closer to allowance, Applicants have amended claim 23 to remove treatment of tumor growth and tumor metastasis. Claim 23 now recites a method of treating a disease or disorder selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, inflammatory disorders of the central nervous system, asthma, allergies, cardiovascular disorders, ateriosclerosis, restenoses, diabetes, damage to organ transplants, and malaria with the instant compounds. Likewise, new claim 104 recites a method for treating melanoma with the instant compounds as supported by the specification, specifically at page 3, lines 9-12, which conforms to the Examiner's requirements. See Office Action at page 4 ("Applicant need to point out in the specification where there is a support including pharmacological data for treating specific type of tumors.").

Applicants respectfully submit that the instant methods are sufficiently enabled since the specification sets forth a reasonable correlation between the activity of the instant compounds and treatment of the recited diseases. See M.P.E.P. § 2107.02 (As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980) (Emphasis applied). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. Nelson v. Bowler, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).)

Here, the specification at pages 1-5 lists a number of references demonstrating that the state of the art recognizes a reasonable correlation between treatment of the covered diseases

and VLA-4 inhibitory activity of the instant compounds, thus setting forth that the instant methods can be practiced without undue experimentation. See M.P.E.P. § 2164.01 (citing In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)).

In the rejection, the Examiner cites Carter, S.K. et al., Chemotherapy of Cancer, second Edition; John Wiley & Son: New York, 1981; appendix C, (Carter et al.) and states that "[t]here is no drug which is broadly effective against all forms of tumors." However, despite Carter et al., there is nothing in the record establishing why the instant compounds would not possess those characteristics that would be effective in treating the recited diseases.

Accordingly, Applicants respectfully submit that the instant methods are adequately enabled based upon the supporting disclosure and information known in the art. Accordingly, reconsideration and withdrawal of the rejection under § 112, first paragraph is respectfully requested.

Claim Rejections under 35 U.S.C. § 112, second paragraph

On pages 4 and 5 of the Office Action, the Examiner has rejected claims 21-24 and 39-103 under 35 U.S.C. § 112, second paragraph. Specifically, the Examiner asserts that ""[i]nflammatory disorder of central nervous system", "which can also contain", "can optionally be", "can optionally stand", "which can also be substituted", "which can also contain" "forms and mixtures" (should be "forms or mixtures"), "and/or", "cannot all simultaneously be" "customary in peptide chemistry", "can be protected", "free functional groups", "allergies", "which can contain", "can be", renders claims indefinite because there no limits and boundaries on claims"". Applicants respectfully traverse the rejection.

Applicants respectfully submit that the terms indicated by the Examiner are clear to those of ordinary skill. Applicants also point out that breadth is not indefiniteness. See M.P.E.P. § 2173.04 (Breadth of a claim is not to be equated with indefiniteness. In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.).

Double Patenting

On pages 5-7 of the Office Action, the Examiner has rejected claims 21-24 and 39-103 under alleged double patenting over claims 1-20 of Serial No. 09/405,843. Applicants respectfully request that the Examiner reserve this rejection until allowable subject matter has been indicated in the instant application, outside of this double patenting rejection.

Conclusion

In view of the foregoing remarks, reconsideration of the application and allowance of all claims is requested. If there are any issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the number below.

Respectfully submitted,

Date: January 25, 2002

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Applicants, therefore, respectfully request that the PTO expunge the 08/971,960 PIDS and return same to applicants.

Respectfully submitted,

January 24, 2002
Date

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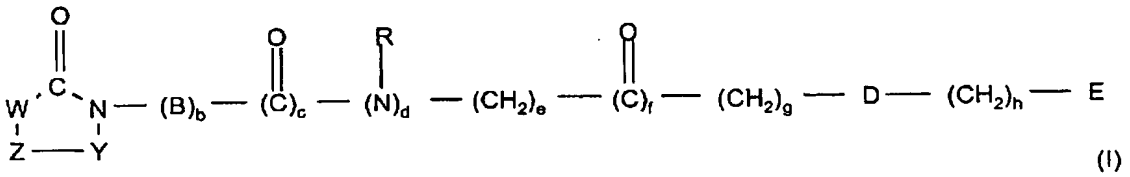
Please renumber claims 73-103 as claims 72-102.

23. **(Twice Amended)** A method for treating a disease or disorder selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, inflammatory disorders of the central nervous system, asthma, allergies, cardiovascular disorders, ateriosclerosis, restenoses, diabetes, damage to organ transplants, **[tumor growth, tumor metastasis,]** and malaria comprising administering to a subject in need thereof an effective amount of a preparation comprising an effective amount of at least one compound of the formula I:



(I)

in which

W is R'-A-C(R^{13});

Y is a carbonyl;

Z is N(R^0);

A is a bivalent radical from the group consisting of (C_1-C_6)-alkylene, (C_3-C_7)-cycloalkylene, phenylene, phenylene-(C_1-C_6)-alkyl, (C_1-C_6)-alkylenephenyl, phenylene-(C_2-C_6)-alkenyl or a bivalent radical of a 5- or 6-membered saturated or unsaturated ring which can contain 1 or 2 nitrogen atoms and can be mono- or disubstituted by (C_1-C_6)-alkyl or doubly bonded oxygen or sulfur;

B is a bivalent radical from the group consisting of (C_1-C_6)-alkylene, (C_2-C_6)-alkenylene, phenylene, phenylene-(C_1-C_3)-alkyl, (C_1-C_3)-alkylenephenyl, where the bivalent (C_1-C_6)-alkylene radical can be unsubstituted or substituted by a radical from the group consisting of (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, (C_3-C_{10})-cycloalkyl-(C_1-C_6)-alkyl, optionally substituted (C_6-C_{14})-

aryl, $(C_6$-$C_{14})$-aryl-$(C_1$-$C_6)$-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl and heteroaryl $(C_1$-$C_6)$-alkyl optionally substituted in the heteroaryl radical;

D is $C(R^2)(R^3)$, $N(R^3)$ or $CH=C(R^3)$;

E is $R^{10}CO$;

R is hydrogen, $(C_1$-$C_8)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, optionally substituted $(C_6$-$C_{14})$-aryl or $(C_6$-$C_{14})$-aryl-$(C_1$-$C_8)$-alkyl optionally substituted in the aryl radical;

R^0 is $(C_3$-$C_{12})$-cycloalkyl, $(C_3$-$C_{12})$-cycloalkyl-$(C_1$-$C_8)$-alkyl, $(C_6$-$C_{12})$-bicycloalkyl, $(C_6$-$C_{12})$-bicycloalkyl-$(C_1$-$C_8)$-alkyl, $(C_6$-$C_{12})$-tricycloalkyl, $(C_6$-$C_{12})$-tricycloalkyl-$(C_1$-$C_8)$-alkyl, optionally substituted $(C_6$-$C_{14})$-aryl, $(C_6$-$C_{14})$-aryl-$(C_1$-$C_8)$-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl, heteroaryl-$(C_1$-$C_8)$-alkyl optionally substituted in the heteroaryl radical, CHO, $(C_1$-$C_8)$-alkyl-CO, $(C_3$-$C_{12})$-cycloalkyl-CO, $(C_3$-$C_{12})$-cycloalkyl-$(C_1$-$C_8)$-alkyl-CO, $(C_6$-$C_{12})$-bicycloalkyl-CO, $(C_6$-$C_{12})$-bicycloalkyl-$(C_1$-$C_8)$-alkyl-CO, $(C_6$-$C_{12})$-tricycloalkyl-CO, $(C_6$-$C_{12})$-tricycloalkyl-$(C_1$-$C_8)$-alkyl-CO, optionally substituted $(C_6$-$C_{14})$-aryl-CO, $(C_6$-$C_{14})$-aryl-$(C_1$-$C_8)$-alkyl-CO optionally substituted in the aryl radical, optionally substituted heteroaryl-CO, heteroaryl-$(C_1$-$C_8)$-alkyl-CO optionally substituted in the heteroaryl radical, $(C_1$-$C_8)$-alkyl-$S(O)_n$, $(C_3$-$C_{12})$-cycloalkyl-$S(O)_n$, $(C_3$-$C_{12})$-cycloalkyl-$(C_1$-$C_8)$-alkyl-$S(O)_n$, $(C_6$-$C_{12})$-bicycloalkyl-$S(O)_n$, $(C_6$-$C_{12})$-bicycloalkyl-$(C_1$-$C_8)$-alkyl-$S(O)_n$, $(C_6$-$C_{12})$-tricycloalkyl-$S(O)_n$, $(C_6$-$C_{12})$-tricycloalkyl-$(C_1$-$C_8)$-alkyl-$S(O)_n$, optionally substituted $(C_6$-$C_{14})$-aryl-$S(O)_n$, $(C_6$-$C_{14})$-aryl-$(C_1$-$C_8)$-alkyl-$S(O)_n$ optionally substituted in the aryl radical, optionally substituted heteroaryl-$S(O)_n$ or heteroaryl-$(C_1$-$C_8)$-alkyl-$S(O)_n$ optionally substituted in the heteroaryl radical, where n is 1 or 2;

R^1 is X-NH-C(=NH)-$(CH_2)_p$ or X^1-NH-$(CH_2)_p$, where p is 0, 1, 2 or 3;

X is hydrogen, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkylcarbonyl, $(C_1$-$C_6)$-alkoxycarbonyl, $(C_1$-$C_{18})$-alkylcarbonyloxy, $(C_1$-$C_6)$-alkoxycarbonyl, optionally substituted $(C_6$-$C_{14})$-arylcarbonyl, optionally substituted $(C_6$-$C_{14})$-aryloxycarbonyl, $(C_6$-$C_{14})$-aryl-$(C_1$-$C_6)$-alkoxycarbonyl which can also be substituted in the aryl radical, $(R^8O)_2P(O)$, cyano, hydroxyl, $(C_1$-$C_6)$-alkoxy, $(C_6$-$C_{14})$-aryl-$(C_1$-$C_6)$-alkoxy which can also be substituted in the aryl radical, or amino;

X^1 has one of the meanings of X or is R'-NH-C(=N-R"), where R' and R" independently of one another have the meanings of X;

R^2 is hydrogen, (C_1-C_8)-alkyl, optionally substituted (C_6-C_{14})-aryl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical or (C_3-C_8)-cycloalkyl;

R^3 is hydrogen, (C_1-C_8)-alkyl, optionally substituted (C_6-C_{14})-aryl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical, (C_3-C_8)-cycloalkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, (C_2-C_8)-alkenylcarbonyl, (C_2-C_8) alkynylcarbonyl, pyridyl, $R^{11}NH$, R^4CO, $COOR^4$, $CON(CH_3)R^{14}$, $CONHR^{14}$, $CSNHR^{14}$, $COOR^{15}$, $CON(CH_3)R^{15}$ or $CONHR^{15}$;

R^4 is hydrogen or (C_1-C_{28})-alkyl which can optionally be mono- or polysubstituted by identical or different radicals $R^{4'}$;$R^{4'}$ is hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di-$((C_1-C_{18}))$-alkyl)aminocarbonyl, amino-(C_2-C_{18})-alkylaminocarbonyl, amino-(C_1-C_3)-alkylphenyl-(C_1-C_3)-alkylaminocarbonyl, (C_1-C_{18})-alkylcarbonylamino-(C_1-C_3)-alkylphenyl-(C_1-C_3)-alkylaminocarbonyl, (C_1-C_{18})-alkylcarbonylamino-(C_2-C_{18})-alkylaminocarbonyl, (C_6-C_{14})-aryl-(C_1-C_8)-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C_1-C_{18})-alkoxy, (C_1-C_{18}) alkoxycarbonyl, optionally substituted (C_3-C_8)-cycloalkyl, halogen, nitro, trifluoromethyl or the radical R^5;

R^5 is optionally substituted (C_6-C_{14})-aryl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical, a mono- or bicyclic 5- to 12-membered heterocyclic ring which can be aromatic, partially hydrogenated or completely hydrogenated and which can contain one, two or three identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur, a radical R^6 or a radical R^6CO-. where the aryl radical and, independently thereof, the heterocyclic radical can be mono- or polysubstituted by identical or different radicals from the group consisting of (C_1-C_{18})-alkyl, (C_1-C_{18})-alkoxy, Halogen, nitro, amino and trifluoromethyl;

R^6 is R^7R^8N, R^7O or R^7S or an amino acid side chain, a natural or unnatural amino acid, imino acid, optionally N-(C_1-C_8)-alkylated or N-$((C_6-C_{14})$-aryl-(C_1-C_8)-alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced

to -NH-CH_2-, and their esters and amides, where hydrogen or hydroxymethyl can optionally stand in place optionally protected free functional groups;

R^7 is hydrogen, (C_1-C_{18})-alkyl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl, (C_1-C_{18})-alkylcarbonyl, (C_1-C_{18})-alkoxycarbonyl, (C_6-C_{14})-arylcarbonyl, (C_6-C_{14})-aryl-(C_1-C_8)-alkylcarbonyl or (C_6-C_{14})-aryl-(C_1-C_{18})-alkyloxycarbonyl, where the alkyl groups can optionally be substituted by an amino group and/or where the aryl radicals can be mono- or polysubstituted, preferably monosubstituted, by identical or different radicals from the group consisting of (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, halogen, nitro, amino and trifluoromethyl, or is a natural or unnatural amino acid, imino acid, optionally N-(C_1-C_8)-alkylated or N-((C_6-C_{14})-aryl-(C_1-C_8)-alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to -NH-CH_2-;

R^8 is hydrogen, (C_1-C_{18})-alkyl, optionally substituted (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_8)-alkyl which can also be substituted in the aryl radical;

R^9 is hydrogen, aminocarbonyl, (C_1-C_{18})-alkylaminocarbonyl, (C_3-C_8)-cycloalkylaminocarbonyl, optionally substituted (C_6-C_{14})-arylaminocarbonyl, (C_1-C_{18})-alkyl, optionally substituted (C_6-C_{14})-aryl or (C_3-C_8)-cycloalkyl;

R^{10} is hydroxyl, (C_1-C_{18})-alkoxy, (C_6-C_{14})-aryl-(C_1-C_8)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C_6-C_{14})-aryloxy, amino or mono- or di-((C_1-C_{18})-alkyl)amino;

R^{11} is hydrogen (C_1-C_{18})-alkyl, $R^{12}CO$, optionally substituted (C_6-C_{14})-aryl-$S(O)_2$, (C_1-C_{18})-alkyl-$S(O)_2$, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical or $R^9NHS(O)_2$;

R^{12} is hydrogen (C_1-C_{18})-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, optionally substituted (C_6-C_{14})-aryl, (C_1-C_{18})-alkoxy, (C_6-C_{14})-aryl-(C_1-C_8)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C_6-C_{14})-aryloxy, amino or mono- or di-((C_1-C_{18})-alkyl)amino;

R^{13} is hydrogen, (C_1-C_6)-alkyl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical or (C_3-C_8)-cycloalkyl;

R^{14} is hydrogen or (C_1-C_{28})-alkyl which can optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di-((C_1-C_{18})-alkyl)-

aminocarbonyl, amino-(C_2-C_{18})-alkylaminocarbonyl, amino-(C_1-C_3)-alkylphenyl-(C_1-C_3)-alkylaminocarbonyl, (C_1-C_{18})-alkylcarbonylamino-(C_1-C_3)-alkylphenyl-(C_1-C_3)-alkylaminocarbonyl, (C_1-C_{18})-alkylcarbonyl-amino-(C_2-C_{18})-alkylaminocarbonyl, (C_6-C_{14})-aryl-(C_1-C_{18})-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C_1-C_{18})-alkoxy, (C_1-C_{18})-alkoxycarbonyl, optionally substituted (C_3-C_8)-cycloalkyl, $HOS(O)_2$-(C_1-C_3)-alkyl, $R^9NHS(O)_2$-(C_1-C_3)-alkyl, $(R^8O)_2P(O)$-(C_1-C_3)-alkyl, tetrazolyl-(C_1-C_3)-alkyl, halogen, nitro, trifluoromethyl and R^5,

R^{15} is R^{16}-(C_1-C_6)-alkyl or R^{16};

R^{16} is a 6- to 24-membered bicyclic or tricyclic radical which is saturated or partially unsaturated and which can also contain one to four identical or different heteroatoms from the group consisting of nitrogen. oxygen and sulfur and which can also be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl and oxo;

b, c, and d are 1;

e is 0, 1, 2, 3, 4, 5 or 6;

f is 0;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0, 1, 2, 3, 4, 5 or 6;

in all their stereoisomeric forms and mixtures thereof in any ratio, and of their physiologically tolerable salts.